Special Considerations in Diabetes and the Metabolic Syndrome

Symposium on Cardiovascular Markers and Surge of Endpoints Symposium

September 23, 2005
Bethesda, MD

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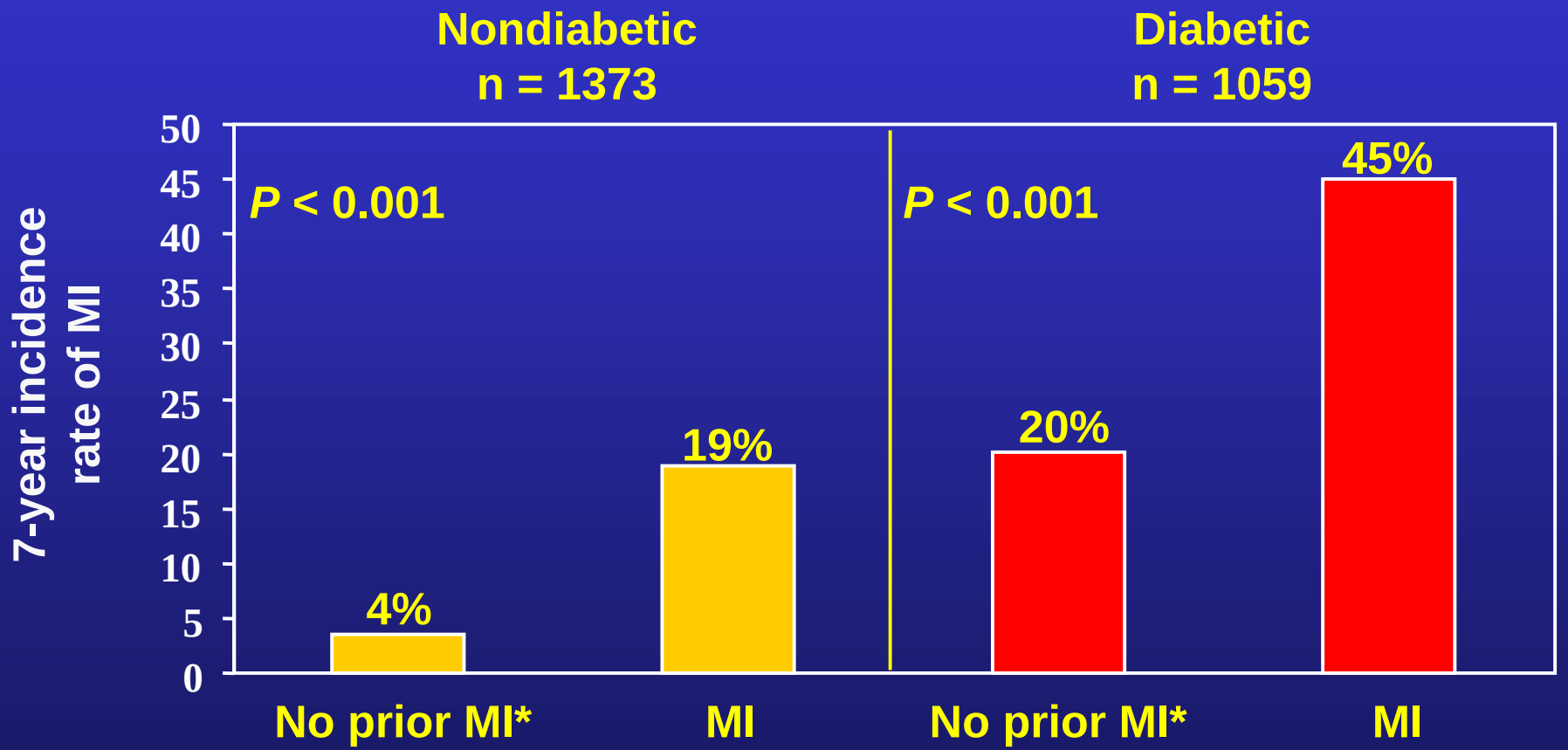
Risk of CVD in Diabetes Mellitus

Type 2 diabetes and CHD: 7-Year Incidence of Fatal/Nonfatal MI (East West Study)

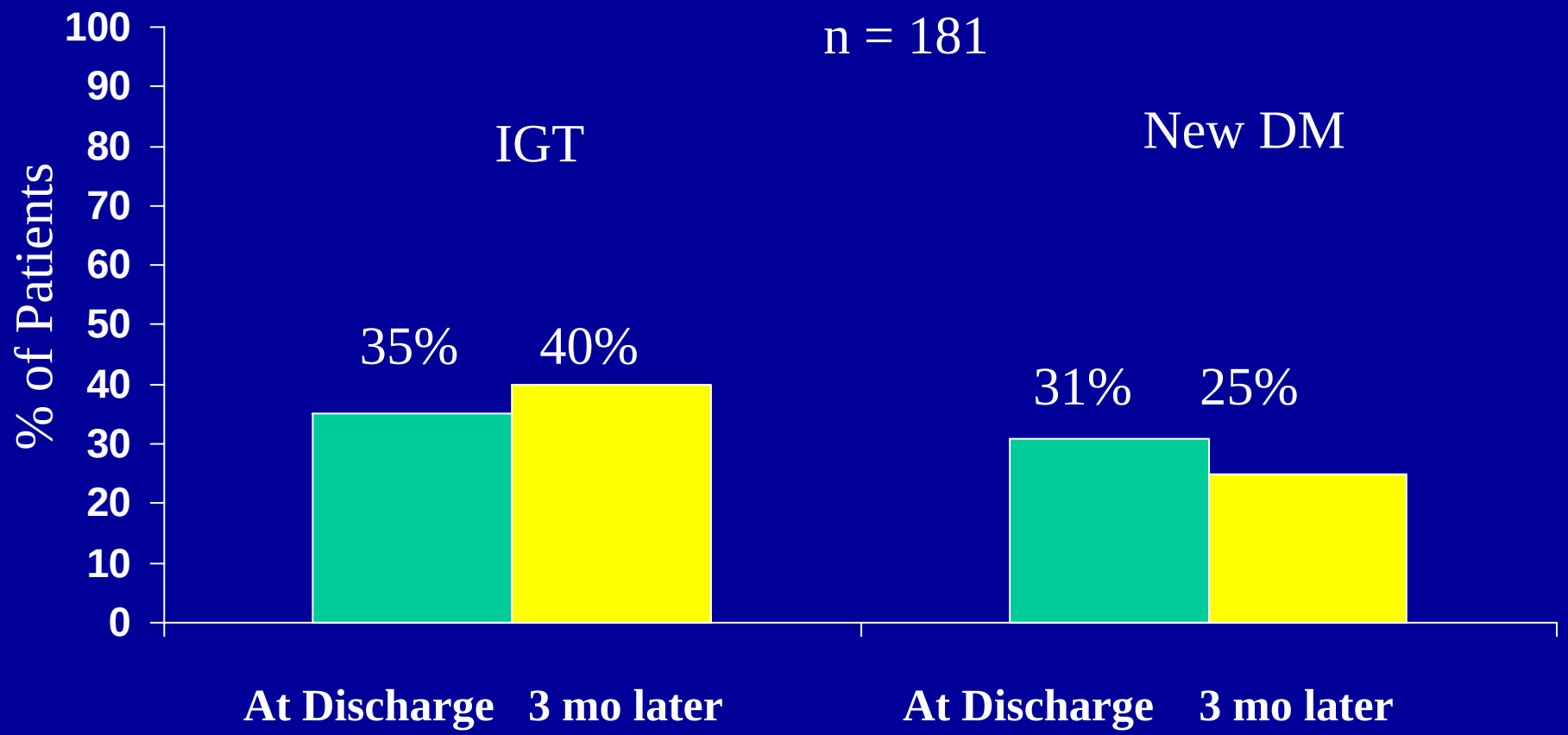


MI = myocardial infarction.

* These patients had no prior MI at baseline.

Haffner SM, et al. *N Engl J Med.* 1998;339:229–234.

Results of OGTT in AMI Patients with Previously Unknown DM



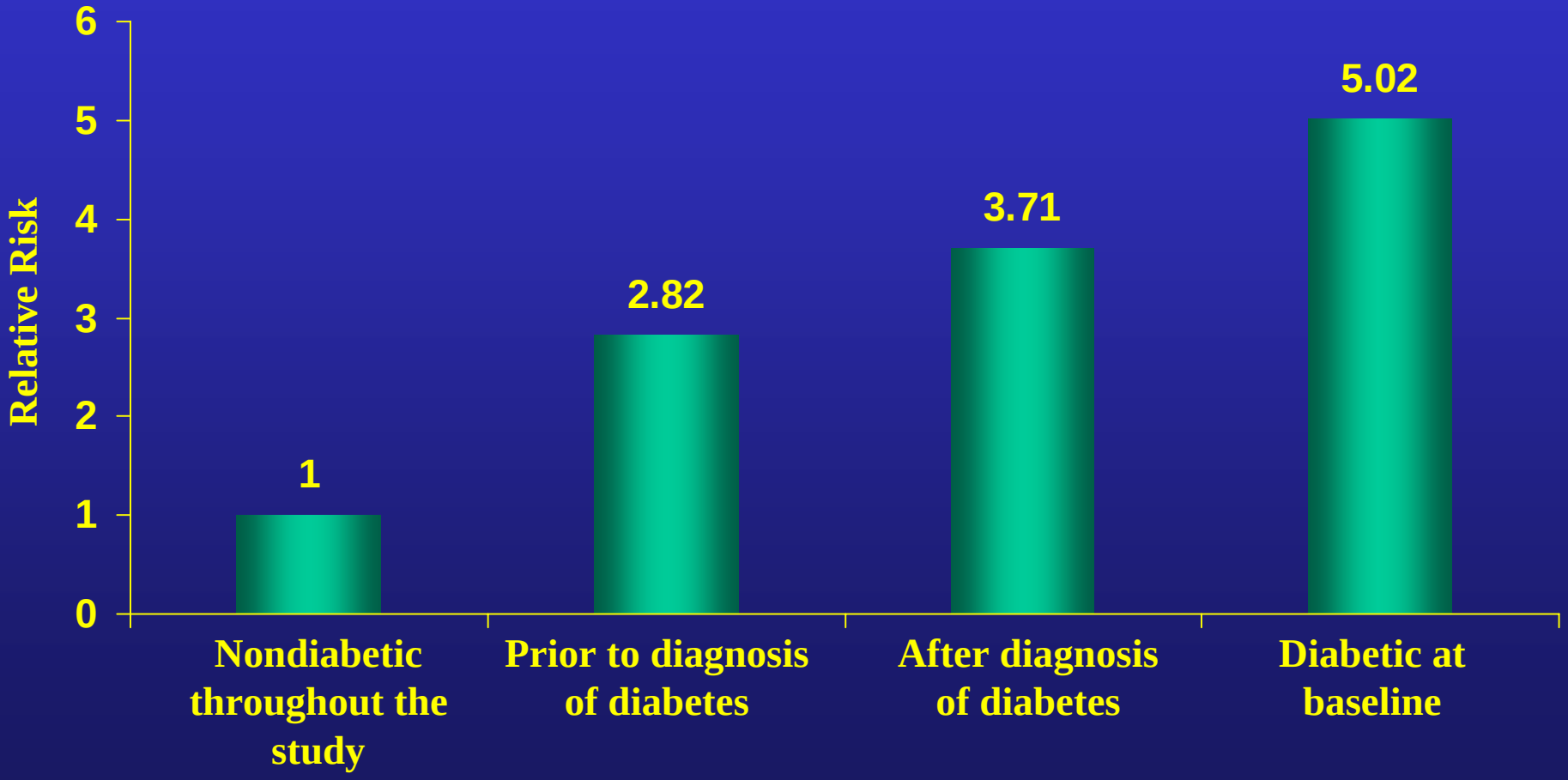
Norhammar A, et al. Lancet 2002;359:2140-44.

Age- and Sex-Adjusted Anthopometric Variables and Cardiovascular Risk Factors at Baseline (Mean) in Subjects with Normal Glucose Tolerance at Baseline According to Conversation Status at 8-Year Follow-Up

	Conversion Status at Follow-Up		
	Diabetes (n=18)	Normal (n=490)	P-Value
Body Mass Index (kg/m2)	28.2± 1.1	27.2± 0.02	.472
Centrality	1.38± 0.09	1.16± 0.2	.076
Triglycerides (mmol/L)	1.83± 0.12	1.28± 0.10	.006
High-density lipoprotein (mmol/L)	1.14± 0.07	1.28± 0.02	.045
Systolic blood pressure (mm Hg)	116.8± 3.0	108.8± 0.8	.004
Fasting glucose (mmol/L)	5.28± 0.1	5.00± 0.02	.032
Fasting insulin (pmol/L)	157± 27	81± 5	.006

Haffner SM et al. JAMA 1990; 263:2893-2898.

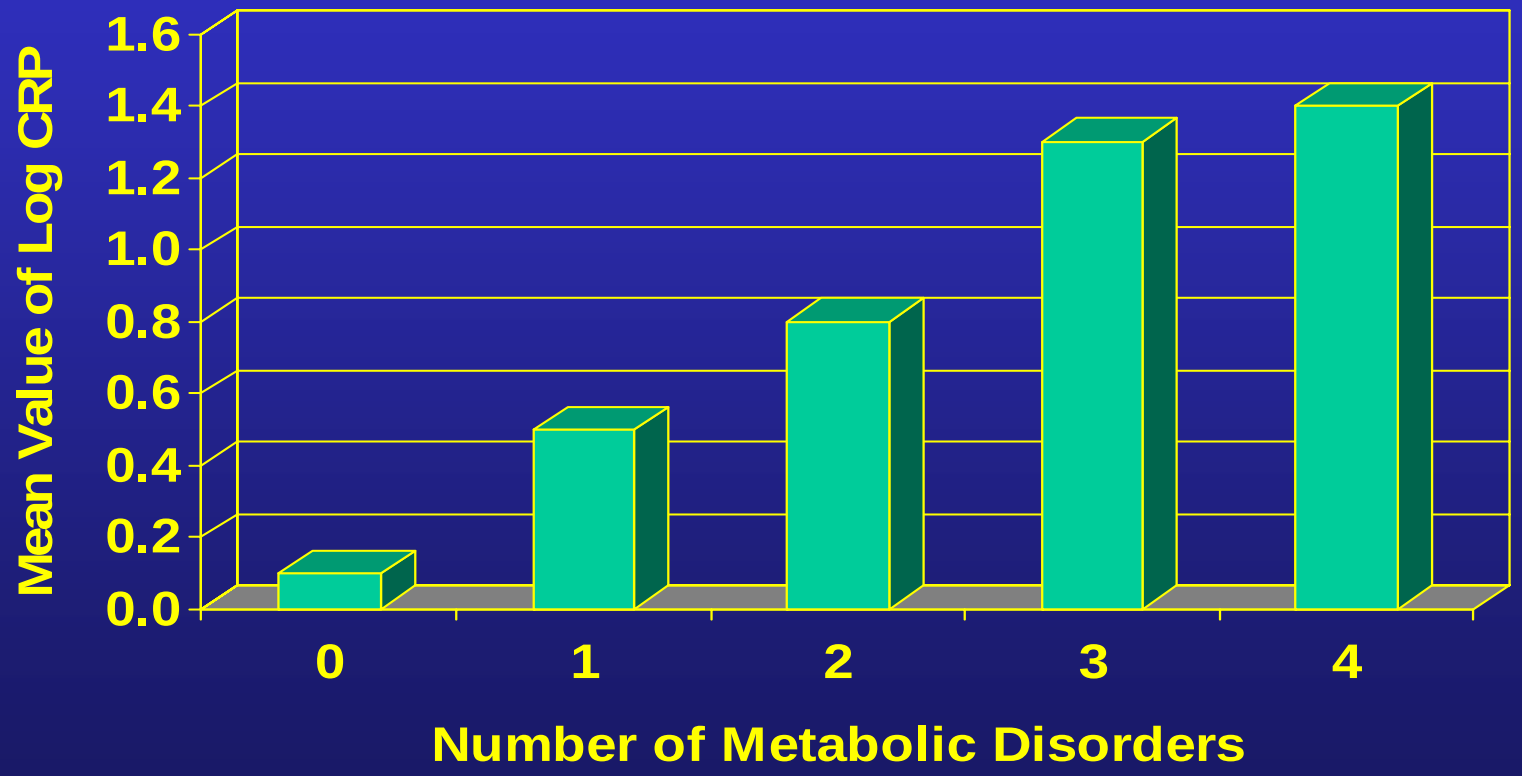
Elevated Risk of CVD Prior to Clinical Diagnosis of Type 2 Diabetes



Hu FB, et al. *Diabetes Care* 2002;25(7):1129-1134.

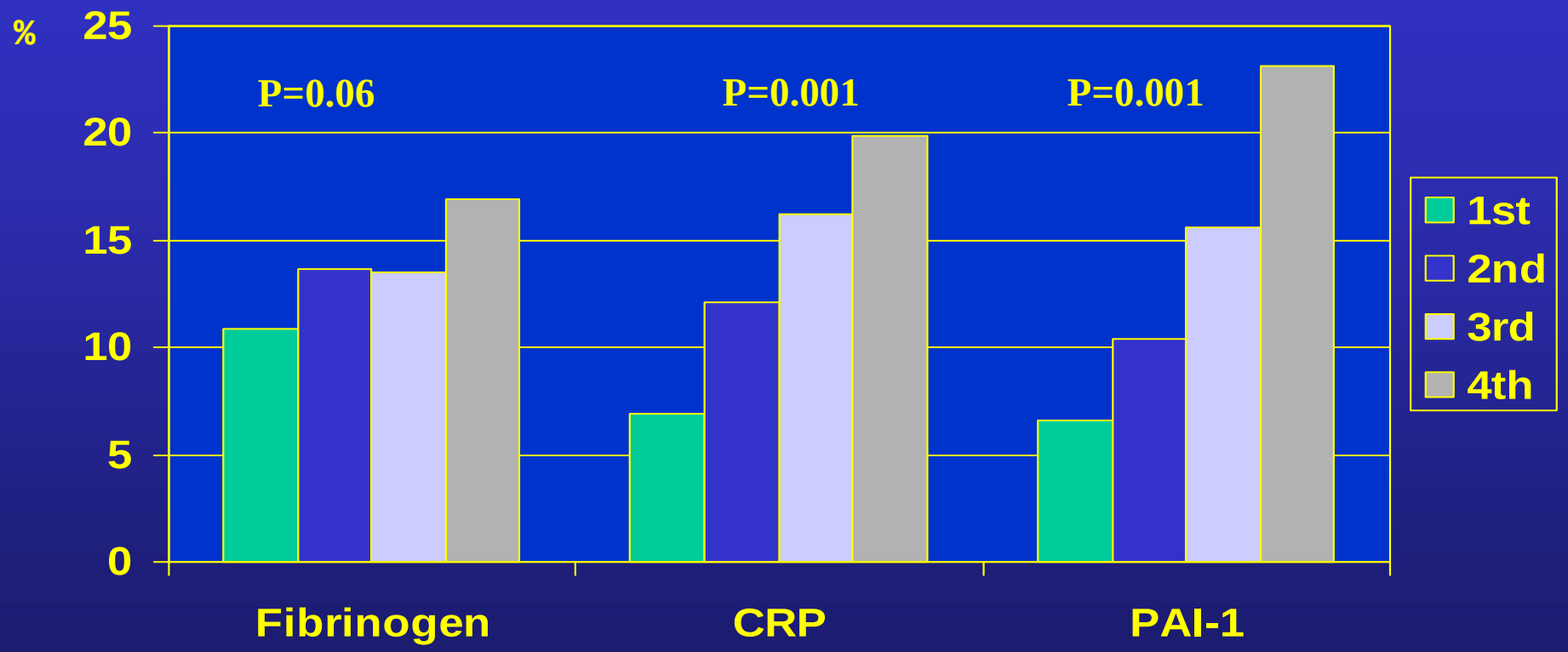
Insulin Resistance, CRP and Diabetes Mellitus

Mean values of CRP by Number of Metabolic Disorders (Dyslipidemia, Upper Body Adiposity, Insulin Resistance, Hypertension)



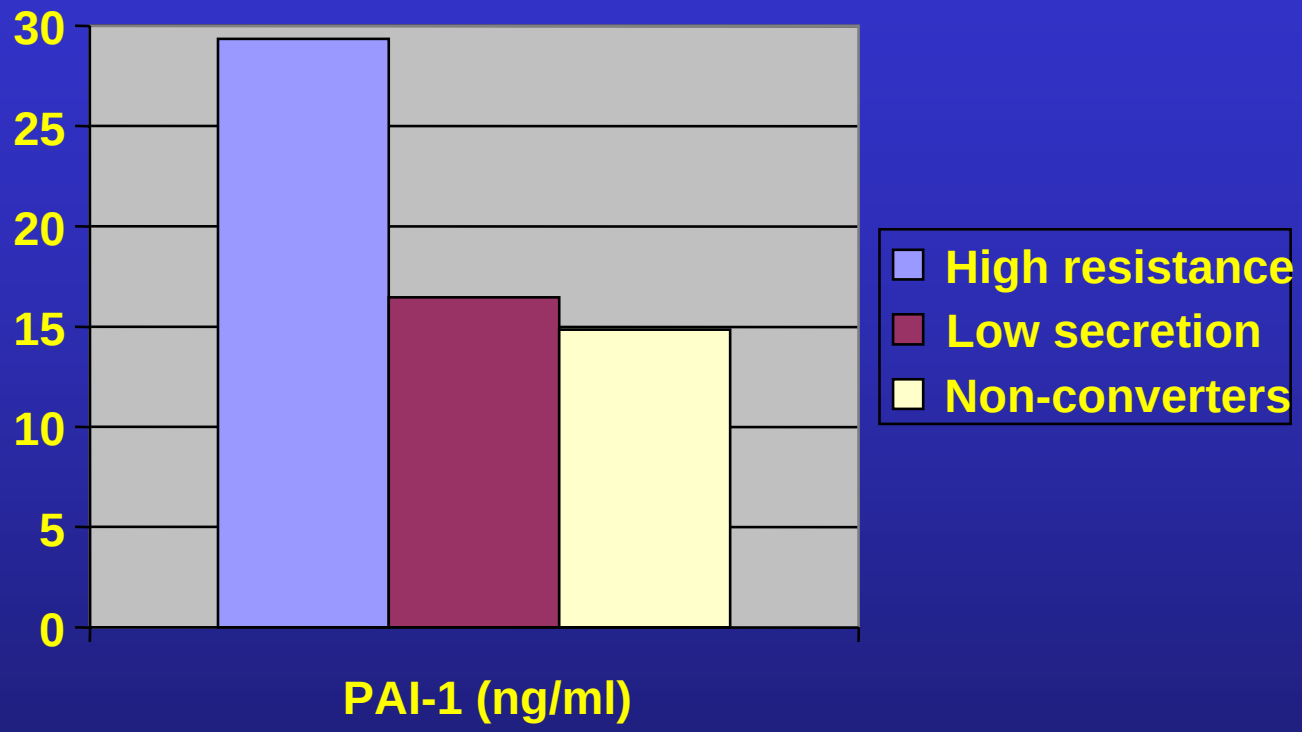
Festa et al. Circulation 102:42-7, 2000.

Five Year Incidence of Type 2 Diabetes Stratified by Quartiles of Inflammatory Proteins: IRAS



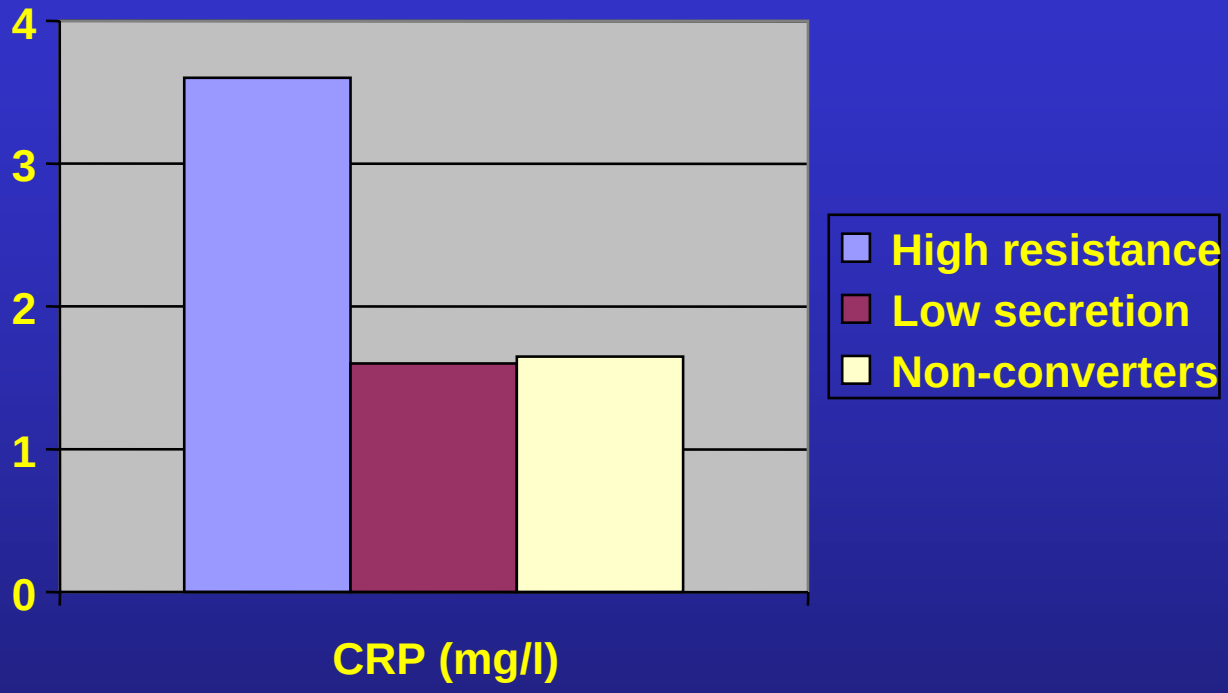
Festa A et al. Diabetes 51:1131-1137, 2002.

PAI-1 in prediabetic subjects: IRAS Study



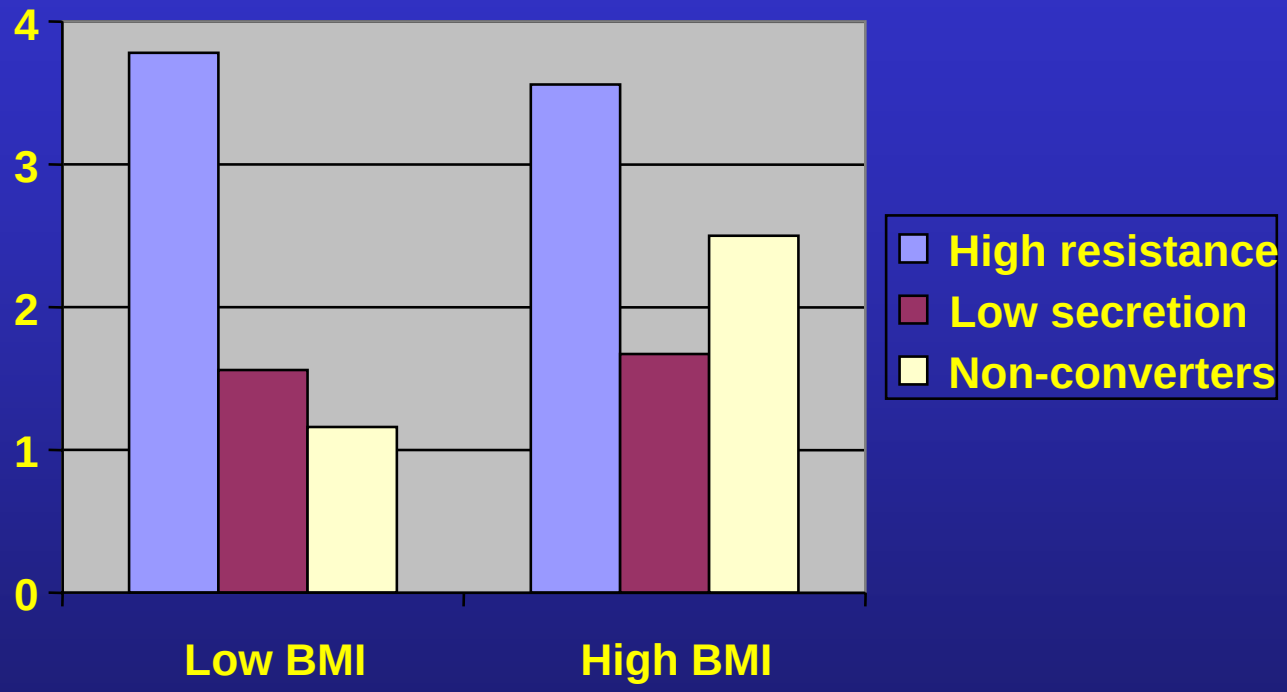
Festa et al. Circulation, 2003; 108: 1822-1830

CRP in prediabetic subjects: IRAS Study



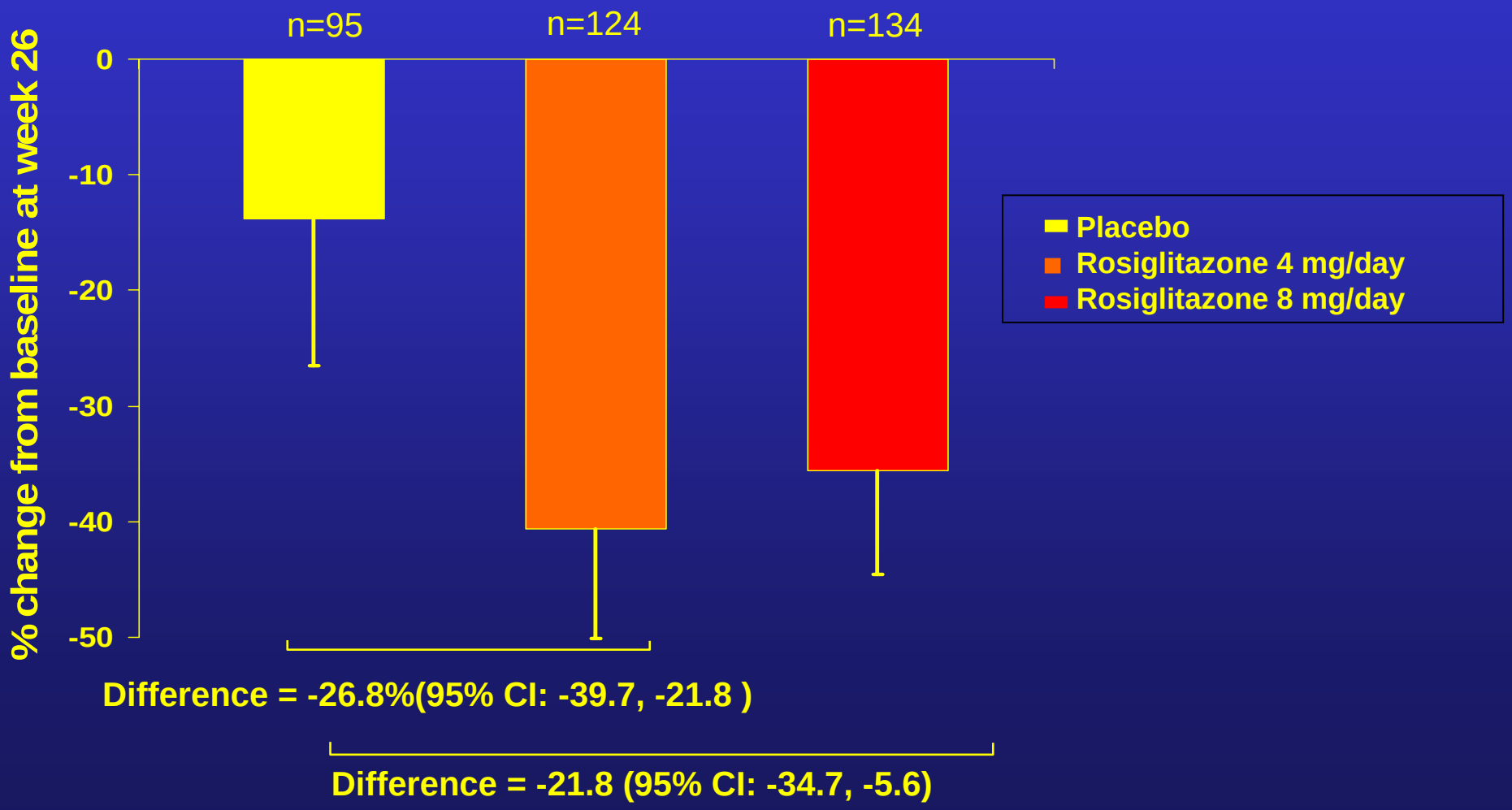
Festa et al. Circulation, 2003; 108: 1822-1830

CRP in relation to metabolic abnormality and BMI in IRAS



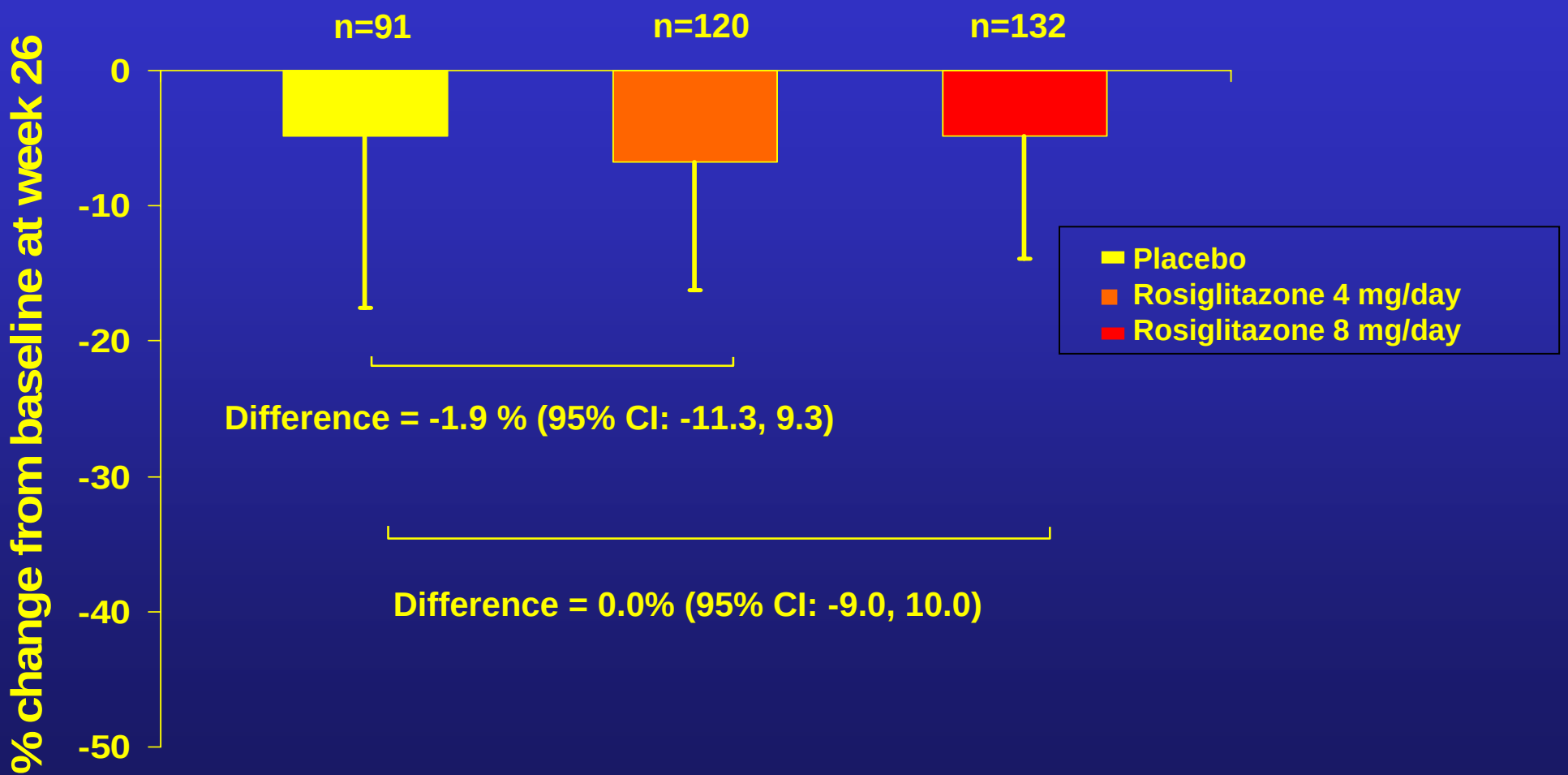
Festa et al. Circulation, 2003; 108:1822-1830

The Effect of Rosiglitazone on CRP



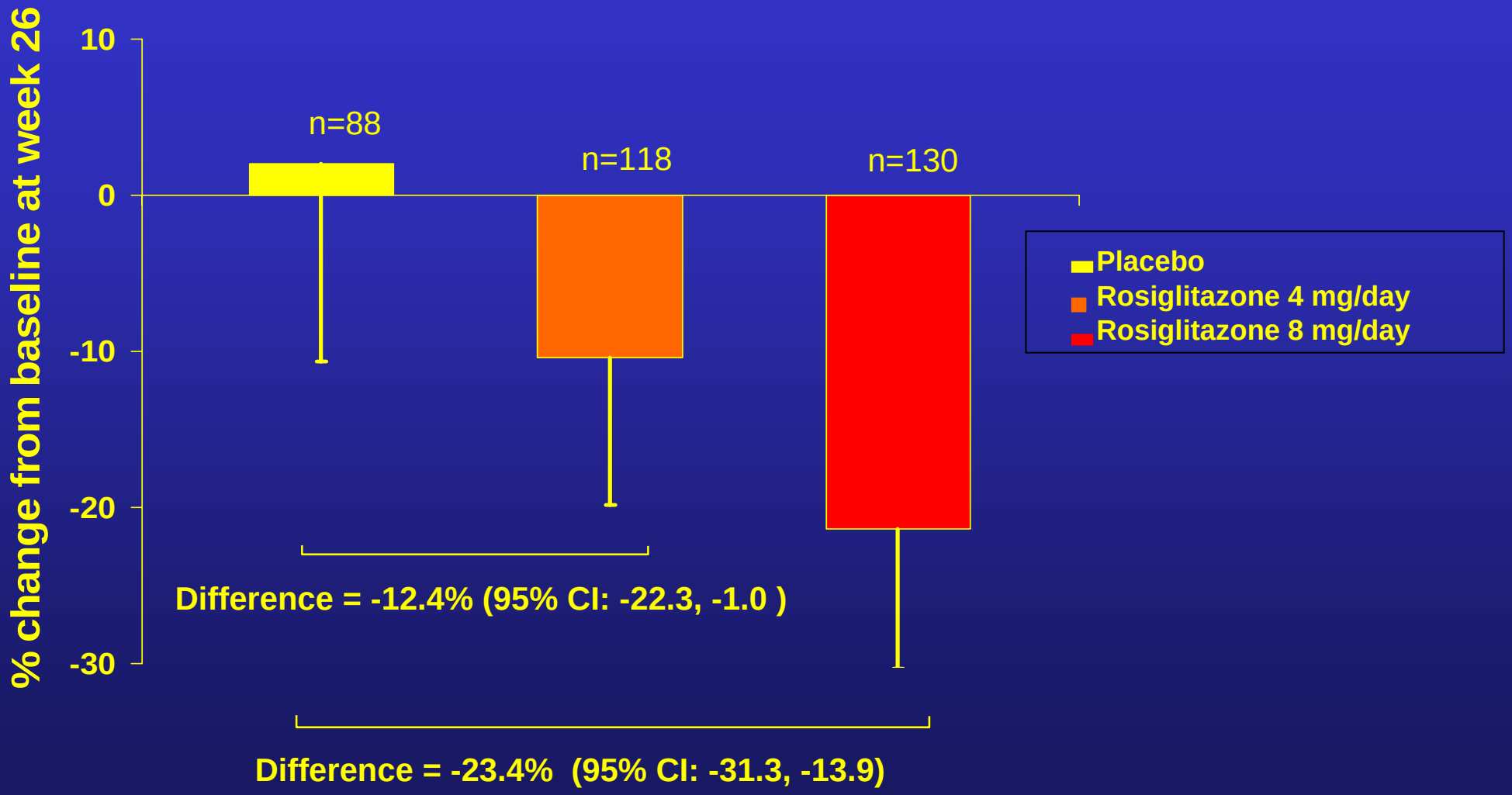
Haffner SM et al. Circulation, 2002; 106:679-684

The Effect of Rosiglitazone on IL-6



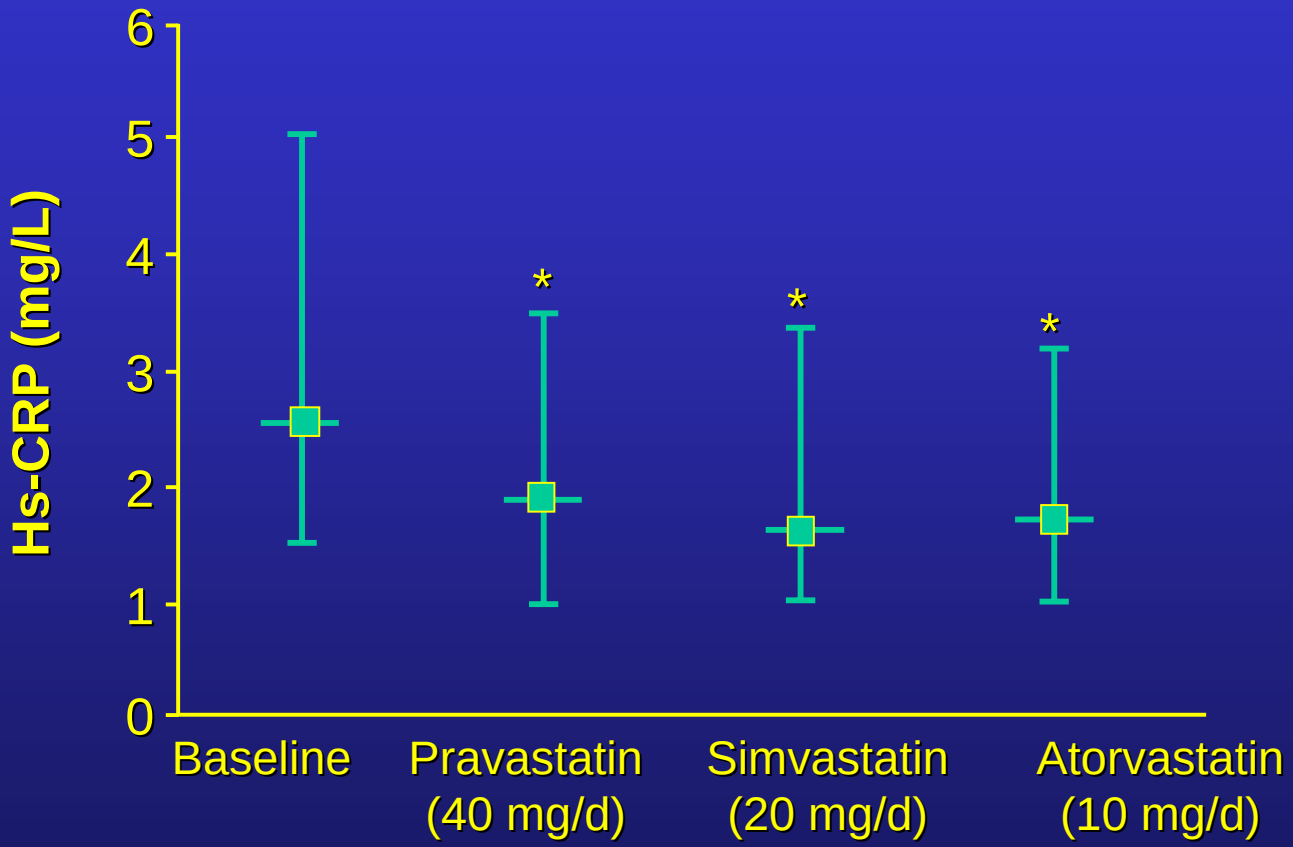
Haffner SM et al. Circulation, 2002; 106:679-684

The Effect of Rosiglitazone on MMP-9



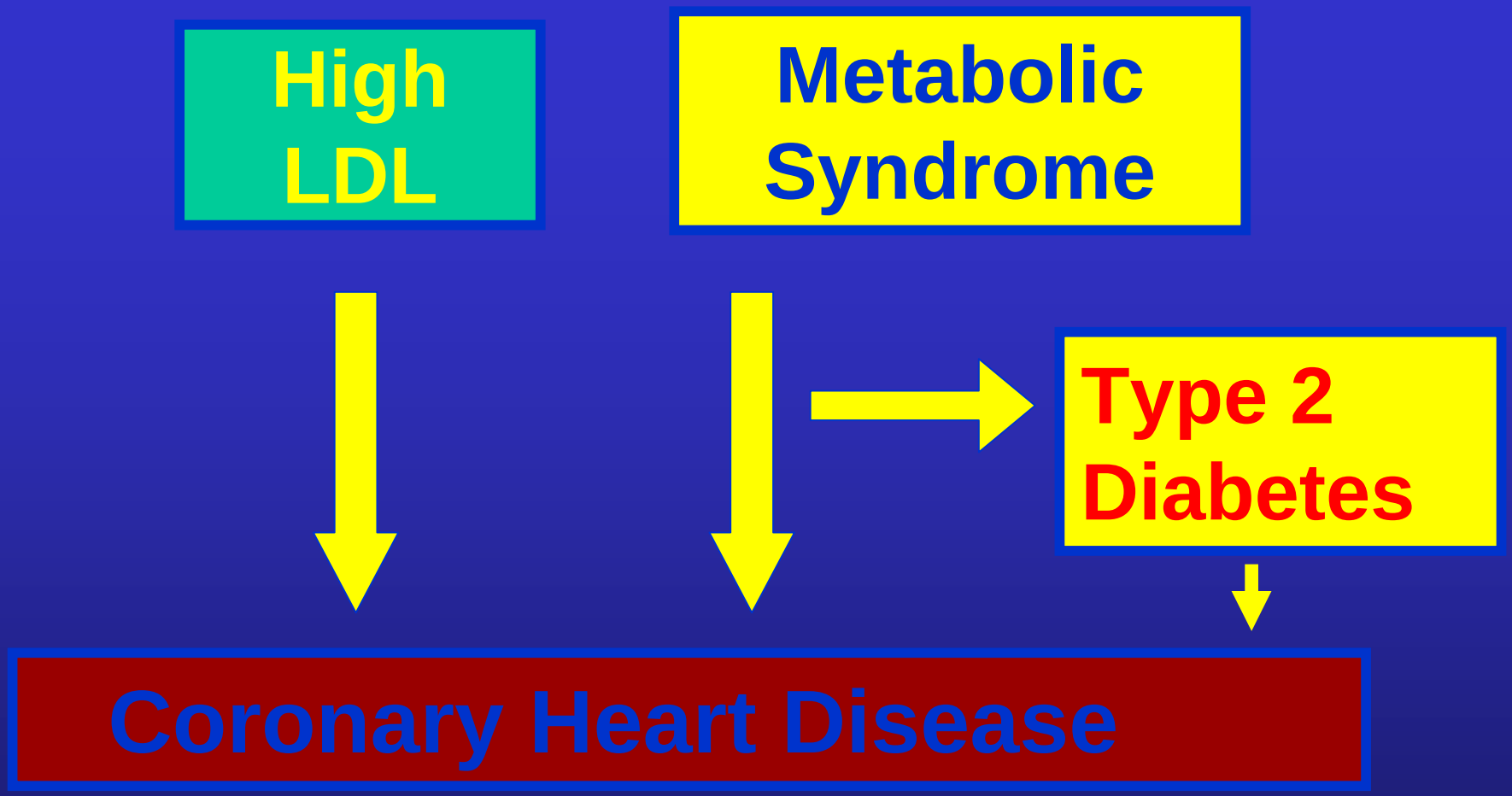
Haffner SM et al. Circulation, 2002; 106:679-684.

Reduction of C-Reactive Protein Levels With Statin Therapy (n=22)



*P<.025 vs baseline

Jialal et al. *Circulation*. 2001;103:1933-1935.



U.S. NCEP ATP III

Conceptual Framework for the Metabolic Syndrome

- Environmental causes are responsible for the epidemic of the metabolic syndrome (NCEP)
  - Treatment: reduce obesity and increase activity
- Insulin resistance is the underlying cause of the metabolic syndrome (WHO)
  - Treatment: a) reduce obesity and increase activity
    b) Insulin sensitizers
- Inflammation is the underlying cause of the metabolic syndrome
  - Treatment: a) reduce obesity and increase activity
    b) Insulin sensitizers
    c) Statins, ACE Inhibitors, ARBs

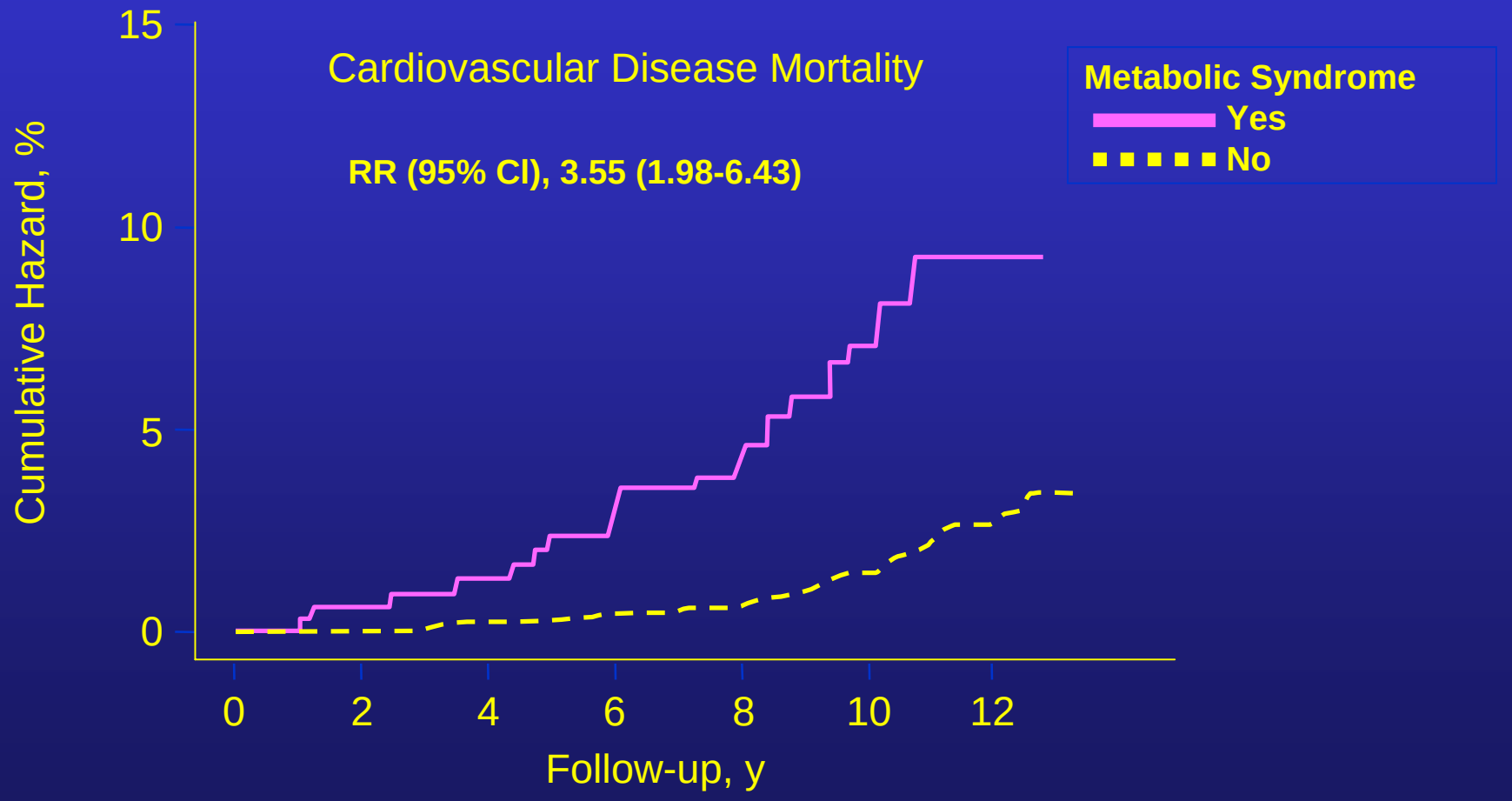
ATP III: The Metabolic Syndrome*

***Diagnosis is established when ≥3 of these risk factors are present.**

Risk Factor	Defining Level
Abdominal obesity (Waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
TG	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 (≥100 (ADA)) mg/dL

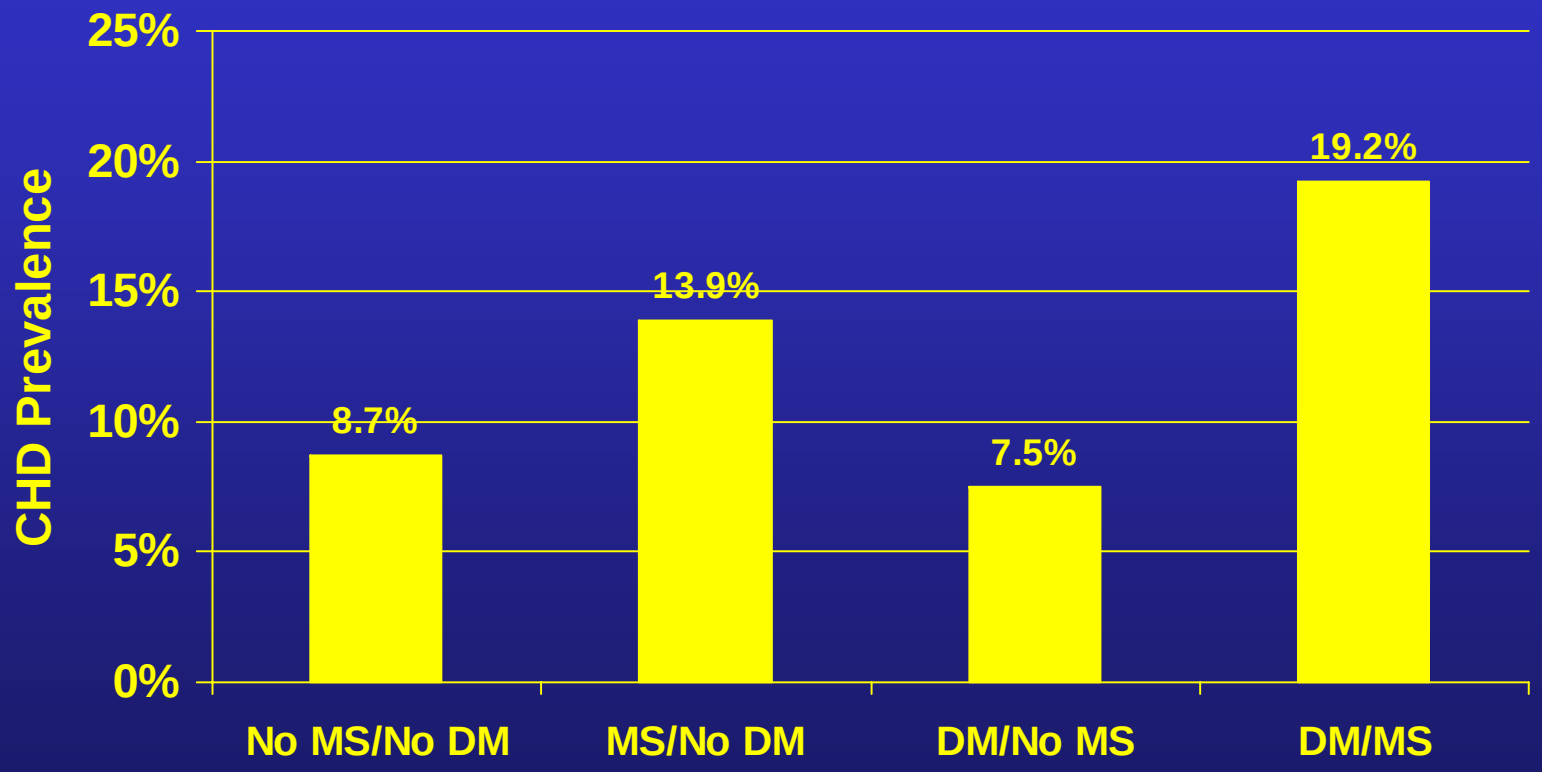
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

Cardiovascular Disease Mortality Increased in the Metabolic Syndrome



Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

Prevalence of CHD by the Metabolic Syndrome and Diabetes in the NHANES Population Age 50+



% of Population =	54.2%	28.7%	2.3%	14.8%

Alexander C, et al. Diabetes 52: 1210-1214, 2003

Hazard Ratio for CVD Mortality (SAHS):

Adjusted for Age and Ethnicity 1: no CVD at baseline

Baseline Status	Women	Men
1. No DM, No NCEP	1.00	1.00
2. No DM, Yes NCEP	2.07 (0.72, 6.00)	1.96 (0.99, 3.88)
3. Yes DM, No NCEP	3.53 (0.75, 16.7)	2.34 (0.70, 7.82)
4. Yes DM, Yes NCEP	8.19 (3.51, 19.1)	3.09 (1.49, 6.43)

Hunt, K. Circulation, 2004; 110:1251-1257

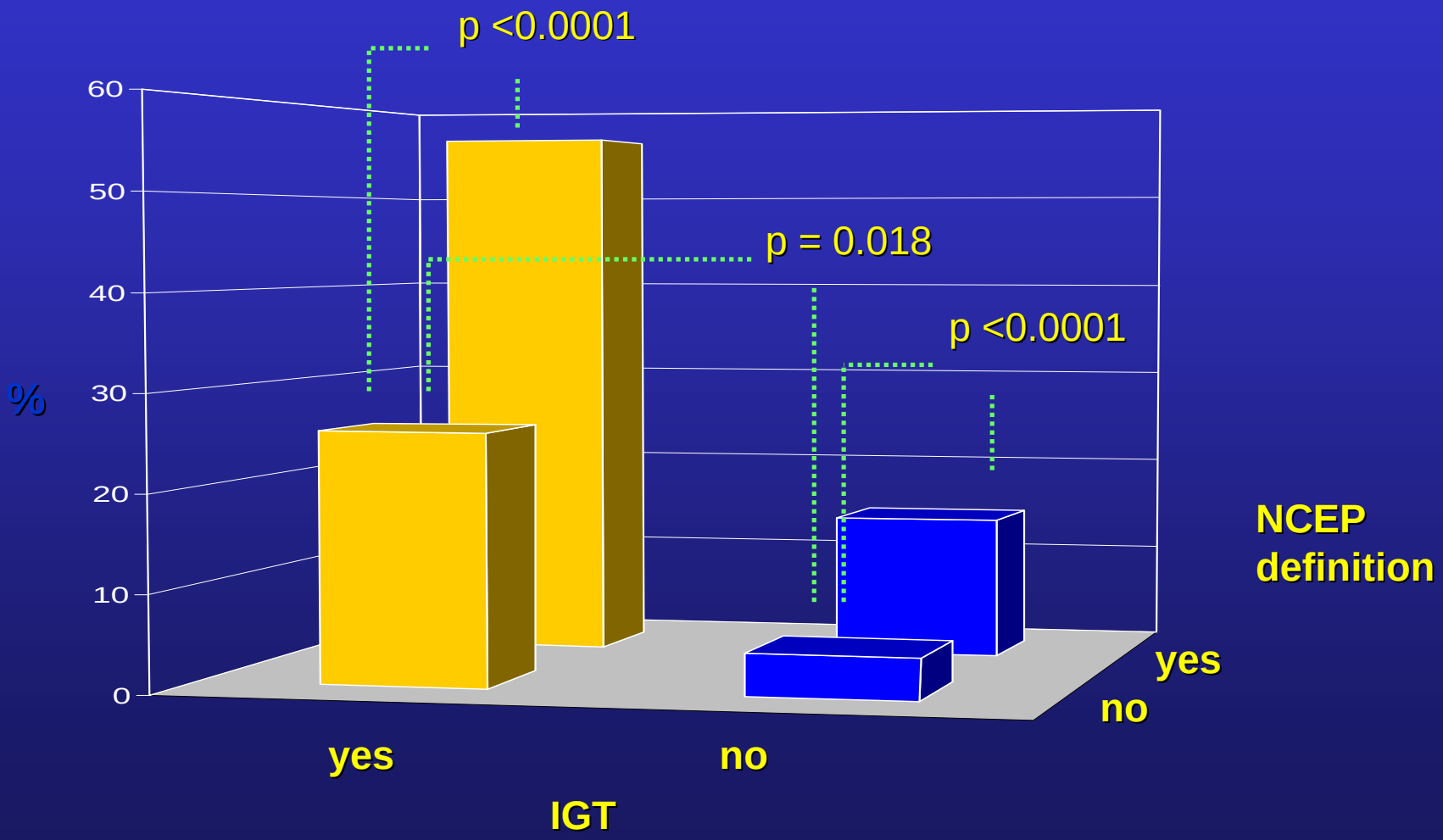
Prediction of CHD Prevalence using Multivariate Logistic Regression: NHANES

Variable	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Waist Circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
HDL Cholesterol	1.74	1.18	2.58
Blood Pressure	1.87	1.37	2.56
Impaired Fasting Glucose	0.96	0.60	1.54
Diabetes	1.55	1.07	2.25
Metabolic Syndrome	0.94	0.54	1.68

Significant predictors of prevalent CHD in red.

Alexander C, et al. Diabetes 52: 1210-1214, 2003

Incident diabetes after stratification by IGT and the metabolic syndrome



Ref. Lorenzo et al, *Diabetes Care, 2003, 26: 3153-3159*

Approaches to Therapy: Metabolic Syndrome

I. Behavioral therapy (weight loss and increased activity)

II. Treat existing risk factors

- a) Should management be intensified over and above global risk?
- b) Yes, but probably not CHD risk equivalent

III. Use of insulin sensitizing therapies in nondiabetic subjects with MS

- a) No for metabolic syndrome alone (no clinical trials)
- b) Do OGTT - three outcomes: 1) DM (treat)
  2) IGT
  3) NGT (no treatment)
- c) Perhaps for IGT subjects (clinical trials available (DPP, STOP-NIDDM, TRIPOD))

What is new with the Metabolic Syndrome?

a) IDF definition of the metabolic syndrome

Lancet, in press, September 2005

b) A critical appraisal of the metabolic syndrome

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes (Kahn R et al, Diabetes Care 28: 2289-2304, 2005)

Abdominal Obesity: Required for Diagnosing the Metabolic Syndrome

IDF criteria of the metabolic syndrome

Similar to the NCEP except required waist circumference

- High waist circumference

Plus any two of

- ↑ Triglycerides (≥ 1.7 mmol/L [150 mg/dL])
- ↓ HDL cholesterol
  - Men < 1.0 mmol/L (40 mg/dL)
  - Women < 1.3 mmol/L (50 mg/dL)
- ↑ Blood pressure ≥ 130 / ≥85 mm Hg
- ↑ FPG (≥ 5.6 mmol/L [100 mg/dL]), or diabetes

International Diabetes Federation (2005), Lancet (in press September 2005)

New IDF Criteria: Abdominal Obesity and Waist Circumference Thresholds

	Men	Women
Europid	≥94 cm (37.0 in)	≥80 cm (31.5 in)
South Asian	≥90 cm (35.4 in)	≥80 cm (31.5 in)
Chinese	≥90 cm (35.4 in)	≥80 cm (31.5 in)
Japanese	≥85 cm (33.5 in)	≥90 cm (35.4 in)

Current NCEP ATP-III criteria: >102 cm (>40 in) in men, >88 cm (>35 in) in women

NCEP 2002; www.idf.org accessed May 28 2005

ADA and EASD Statement

The term "metabolic syndrome" refers to a clustering of specific cardiovascular disease (CVD) risk factors whose underlying pathophysiology is thought to be related to insulin resistance. Since the term is widely used in research and clinical practice, we undertook an extensive review of the literature in relation to the syndrome's definition, underlying pathogenesis, and association with CVD and to the goals and impact of treatment. While there is no question that certain CVD risk factors are prone to cluster, we found that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker.

ADA and EASD Statement (continued)

Our analysis indicates that too much critically important information is missing to warrant its designation as a "syndrome." Until much needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the "metabolic syndrome."

(Kahn R et al, Diabetes Care 28: 2289-2304, 2005)